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## Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance



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### ABSTRACT

**Background:** Safety of HPV vaccines is still in question due to reports of autoimmune diseases (ADs) following HPV immunization.

**Objectives:** To assess the risk of ADs associated with HPV vaccination of female adolescents/young adults in France.

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**Methods:** Systematic prospective case-referent study conducted to assess the risks associated with real-life use of HPV vaccines. Cases were female 11–25 years old with incident ADs [central demyelination/multiple sclerosis (CD/MS), connective tissue disease (CTD), Guillain-Barré syndrome (GBS), type-1 diabetes (T1D), autoimmune thyroiditis (AT), and idiopathic thrombocytopenic purpura (ITP)]. Cases were consecutively and prospectively identified at specialized centers across France (2008–2014) and individually matched by age and place of residence to referents recruited in general practice. Risk was computed using multivariate conditional logistic regression models adjusted for family history of ADs, living in France (north/south), co-medications and co-vaccinations.

**Results:** With a total of 478 definite cases matched to 1869 referents, all ADs combined were negatively associated to HPV vaccination with an adjusted odds ratio of 0.58 (95% confidence interval: 0.41–0.83). Similar results were obtained for CD/MS, AT, CT, and T1D, the last two not reaching statistical significance. No association was found for ITP and GBS. Sensitivity analyses combining definite and possible cases with secondary time window showed similar results.

**Conclusion:** Exposure to HPV vaccines was not associated with an increased risk of ADs within the time period studied. Results were robust to case definitions and time windows of exposure. Continued active surveillance is needed to confirm this finding for individual ADs.

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## 1. Introduction

Human papilloma virus (HPV) is one of the most common sexually transmitted infections worldwide [1]. The two HPV vaccines available at the time of the study, the HPV-6/11/16/18 vaccine (*Gardasil*<sup>®</sup>, Merck & Co., Inc) and the HPV-16/18 AS04-adjuvanted vaccine (*Cervarix*<sup>®</sup>, GSK Vaccines), protect against HPV types 6, 11, 16, and 18 and HPV types 16 and 18, respectively. HPV types 16 and 18 are known to cause cervical lesions and are responsible for up to 80% of all cervical cancers, the third most frequent type of female cancer [2] while non-oncogenic HPV types 6 and 11 are responsible for more than 90% of genital warts [3]. The HPV-6/11/16/18 vaccine is the most widely used vaccine in France [4].

While proven effective, the safety of HPV vaccines is in doubt on the basis of reported adverse effects associated to autoimmune events [5] hypothetically connected to molecular mimicry mechanism [6]. However, several studies conducted to date have not been able to provide robust evidence to support these safety concerns [7], which have been reported as barriers to preventive HPV vaccination but justify continued surveillance of autoimmune diseases (ADs) following exposure to HPV vaccines [8].

The Pharmacoepidemiologic General Research eXtension (PGRx) is an ongoing information system developed to assess risks of rare or delayed health events associated with real-life use of medicines and vaccines. The PGRx-Autoimmune Disease (PGRx-AD) registry systematically collects incident cases of autoimmune diseases (ADs) through a network of board-certified specialists and a pool of referents (controls) consulting General Practitioners (GP), from which cases can be matched to referents, allowing for case-referent analyses. The system has also been used to assess the risk of ADs with the quadrivalent HPV-6/11/16/18 vaccine [9]. The objective of this follow-up study was to assess the risk of ADs following exposure to HPV vaccines for over 6.5 years across France as requested by the French health authorities (*Haute Autorité de Santé*).

## 2. Methods

### 2.1. Study population

Cases and referents were recruited prospectively using the PGRx information system between April 2008 and October 2014 (NCT01498627). Cases were recruited consecutively in a network of 168 specialized centers (internal medicine, neurology,

rheumatology, pediatric, endocrinology, and dermatology) from university and general hospitals participating in the PGRx-AD registry across metropolitan France [10]. Recruiting centers were randomly audited during the recruitment period to ensure exhaustive inclusion of cases. Referent-patients were recruited by a network of 236 GPs and pediatricians, all from across metropolitan France, participating in the “PGR-GP” registry. Patients were offered participation regardless of their reason for consulting a physician.

Eligibility criteria for participating in the present study were similar in cases and referent-patients: (1) female gender; (2) aged 11–25 years; (3) living in France; (4) able to undergo a telephone interview in French (the participant herself or her parents); and (5) consenting to participate to the study (parental consent for minor participants).

### 2.2. Case definition and ascertainment

Cases were defined as patients with a first incident clinical manifestation in their lifetime compatible with one of the six following ADs: (1) central demyelination and multiple sclerosis (CD/MS), (2) connective tissue diseases (CTD) – including lupus, chronic inflammatory arthritis, juvenile idiopathic arthritis, rheumatoid arthritis, myositis, and undetermined connective tissue disease – (3) Guillain-Barré syndrome (GBS), (4) type 1 diabetes (T1D), (5) autoimmune thyroiditis (AT), and (6) idiopathic thrombocytopenic purpura (ITP). Each AD was defined according to international conventions [11–17]. Patients with a lifetime history of the AD suspected at inclusion were excluded.

Then, cases were classified as definite, possible or rejected by physicians on the basis of their evolution over the twelve months following diagnosis. When concerns of uncertainty were raised for cases, two physicians, blinded to the vaccination status were requested to independently review the cases.

### 2.3. Referents and matching

Referents were defined as patients meeting the eligibility criteria above, but with no lifetime history of any of the ADs under study. An average of four referents were matched to each case by: (1) age (best match available within a maximum range of 2 years as follows: cases  $\leq 17$  years-old: age of referent  $\pm 1$  month,  $\pm 3$  months,  $\pm 6$  months,  $\pm 1$  year from age of case; and cases  $\geq 18$  years-old: age of referent  $\pm 1$  year,  $\pm 2$  years from age of case), (2) place of residence (North vs. South of France) and (3) index date (defined for cases as

the date of the first symptoms evocative of AD and for referents as the date of recruitment).

No estimated sample size was calculated based on a *a priori* hypothesis; instead, surveillance goal surveying was established if an unusual accrual, such as any large series of incident cases of AD in specialized centers occurred, coinciding with the point in time when one-third of the participants were getting vaccinated against HPV.

#### 2.4. Exposure to HPV vaccination

In cases and referents, information on all medications (including vaccines and medication over-the-counter) used in the 24 months preceding index date, were collected through a structured and standardized telephone interview. This telephone interview was scheduled within the 45 days after recruitment and managed by trained interviewers who were blinded to the case/referent status of patients. Parents were interviewed for children younger than 18 years old. To facilitate remembering the medications used, an interview guide was provided to participants and their parents prior to the telephone interview. Exposure to HPV vaccination was also informed by physicians, in cases and referents and reported using an electronic case notification form.

Exposure to HPV vaccines was considered as a “confirmed exposure” when either patients or physicians provided a tangible proof for HPV vaccination: vaccine batch number, vaccination booklet, prescription noted in health medical record, pharmacist’s report, or any other type of certificate of HPV vaccination. When no record of HPV vaccination was available from either patient or physician reports, it was considered as “confirmed non-exposure”; whenever there was a conflict, both patients and physicians were contacted to confirm non exposure. In our study population, HPV vaccination could be confirmed in 92% of exposed cases and 95% of exposed referents. Comparison of physician records and patient’s self-reporting of HPV vaccination showed a high level of agreement between the two sources of information (99.7% and 98.4% of agreement for the cases and referents, respectively) [18].

#### 2.5. Time windows for defining exposure to HPV vaccine

The definition of the primary time window for exposure to HPV vaccine (any dose) prior to the index date varied across ADs: 24 months for CD/MS, CTD, T1D and AT, 6 months for ITP and 2 months for GBS. Those time windows were determined by the study scientific committee so as to best capture a potential association between the HPV vaccine and a determined AD. A participant was defined as exposed to HPV vaccine if she was given at least one shot of the vaccine within the time window of interest. A secondary time window, defined as exposure to any HPV vaccine before the index date, was used in sensitivity analysis.

#### 2.6. Potential confounders

Potential confounders of the relation between exposure to HPV vaccine and incidence of AD were defined *a priori* based on prior knowledge and clinical experience. First, age, place of residence and index date were used as matching variables. Second, ethnicity and lower socioeconomic status were found to be associated to HPV vaccination rate [19,20]; HPV vaccination may also be associated with higher rates of prior vaccination to protect against other infections; increased exposure to estrogenic compounds (e.g., oral contraceptives) was found, on the one hand, to be a risk factor for developing lupus [21] and on the other hand, is associated with an increased risk for developing another AD; family history of AD in first-degree relatives may increase the risk of developing an AD

[21]. The potential confounders included in our study were: ethnicity, approximated by parents’ place of birth (Northern Europe or North America: both parents/none/mixed), personal history of AD (yes/no), family history of AD in first-degree relatives (yes/no), vaccine protection against other pathogens in the last 2 years (yes/no), and use of oral contraceptives (yes/no).

#### 2.7. Statistical methods

All statistical tests were two-sided with a type-I error set to 5%. First, descriptive parametric statistics were used to compare cases and referents. Second, the association between the odds of AD (all ADs together) and HPV vaccination during the primary time window of exposure was explored using a multivariate conditional logistic regression model, controlling for the above-listed potential confounders and providing odds ratio (OR) and corresponding 95% confidence interval (95%CI). Third, sub-group analyses were performed to explore the association between HPV vaccination and the odds of each type of AD, one multivariate conditional logistic regression model being built for each AD. For these main analyses, only “definite” cases and their matched referents were included. Finally, sensitivity analyses were performed, using both “definite” and “possible” cases of AD (and their matched referents) as well as the secondary time window defined above. Statistical analyses were performed using the SAS software version 9.3 (SAS Institute, North Carolina, USA).

#### 2.8. Ethics committee approval

This study was approved by the Ethics Review Committee of Paris-Ile de France III (Comité de Protection des Personnes Ile de France III) and the French Data Protection Authority (Commission Nationale de l’Informatique et des Libertés). All participants or their parents gave their written consent. Physicians were compensated for inviting and recruiting patients, but not patients.

### 3. Results

#### 3.1. Recruitment and study sample characteristics

The 168 specialized centers participating in the PGRx-AD network identified 569 eligible cases, of which 510 (89.6%) were included and matched to at least one referent. Twelve months after their inclusion, there were 478 definite cases and 32 possible cases (as classified independently by the two experts). A total of 1953 eligible patients from the PGRx-GP pool of referents were matched to cases (1869 matched to definite cases). Cases and referents had a mean age of 20.1 and 19.9 years, respectively, and were almost equally distributed between the north and south of France (Table 1).

Besides matching factors, cases were also similar to referents with respect to living status, main occupation, and immunization status regarding vaccines other than HPV administered within 24 months before index date. Cases were statistically different from referents as to parental origin with respectively 56.7% and 76.8% born to parents originally from Northern Europe or North America, personal history or family (1st degree) history of AD (14.7% and 8.6%, respectively), and use of oral contraceptives (46.7% and 58%, respectively).

Of the two HPV vaccines available in France during the study period, HPV-16/18 and HPV-6/11/16/18, the latter was the most prescribed (95.3% in this sample, which was built to be representative of general use in France). Among the 657 (26.7%) patients administered vaccines other than HPV in the past 24 months, 430 (65.4%) were vaccinated against “diphtheria, tetanus, poliomyelitis,

**Table 1**  
Comparison of all cases (definite and possible) with their matched referents.<sup>a</sup>

	Cases (definite and possible) N = 510 (%) n (%)	Referents <sup>b</sup> N = 1953 n (%)	p-value
<b>Matching variables</b>			
<b>Age (in years), mean (SD)</b>	20.1 (3.7)	19.9 (3.6)	NA
<b>Region of residence in France</b>			
North	273 (53.5)	1004 (51.4)	
South	237 (46.5)	949 (48.6)	NA
<b>Sociodemographic and lifestyle characteristics</b>			
<b>Place of parental birth</b>			
Both Northern Europe or North America	289 (56.7)	1500 (76.8)	
Both Other	141 (27.6)	176 (9.0)	
Mixed or Missing	80 (15.7)	277 (14.2)	<0.05
<b>Living status</b>			
Lives with at least one person	454 (89.0)	1734 (88.8)	0.88
<b>Main occupation</b>			
Student	293 (57.5)	1205 (61.7)	
Not student, employed	160 (31.4)	557 (28.5)	
Not student, unemployed	57 (11.2)	191 (9.8)	0.21
<b>Smoking</b>			
Current smoker	141 (28.0)	624 (32.0)	
Former smoker (stopped smoking for $\geq 1$ year)	25 (5.0)	68 (3.5)	
Never smoked	338 (67.1)	1261 (64.6)	
Missing/choose not to answer	6	0	0.09
<b>Alcohol consumption</b>			
Daily or almost daily	1 (0.2)	6 (0.3)	
At least once per week	40 (8.0)	131 (6.7)	
Occasionally or never	462 (91.8)	1816 (93.0)	
Missing/choose not to answer	7	0	0.57
<b>Personal and family history of AD</b>			
Personal or family <sup>c</sup> (in first-degree relatives) history of any AD	75 (14.7)	141 (7.2)	<0.05
<b>Medication and vaccine utilization, within 24 months before index date</b>			
Oral contraceptive(s)	238 (46.7)	1133 (58.0)	<0.05
Vaccine(s) other than HPV	134 (26.3)	523 (26.8)	0.94
<b>HPV vaccines</b>			
Any HPV vaccine	52 (10.9)	421 (22.5)	
HPV-16/18 vaccine	2 (0.4)	20 (1.0)	
HPV-6/11/16/18 vaccine	50 (9.8)	401 (20.5)	0.48

Abbreviations: AD, autoimmune disease; HPV, human papilloma virus; NA, not applicable; SD, standard deviation.

<sup>a</sup> Referents were matched to cases on age, place of residence (North or South of France) and index date.

<sup>b</sup> Theoretical number of referents derived from the weighted proportion (results for referents were weighed on the number of matched referents per case).

<sup>c</sup> Family history of AD included the AD of interest and rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis.

and pertussis”, 170 (25.9%) against “hepatitis” (mainly HBV), and 130 (19.8%) received a flu vaccine; other vaccines were used in less than 10% of patients (meningitis; tuberculosis; measles, mumps and rubella; etc.).

### 3.2. Risk of ADs and exposure to HPV vaccines

In the primary time window, 10.9% of AD cases and 22.5% of their matched referents had been exposed to HPV vaccine (Table 2). Exposure to HPV vaccines was associated with decreased odds of ADs (all combined); adjusted OR of 0.58 [95%CI: 0.41–0.83]. Similar apparent protective effects were observed for CD/MS and AT, and for CTD and T1D albeit not statistically significant in the two latter ADs. No association was found with ITP and estimation of risks could not be calculated for GBS as there were no cases of exposure to a HPV vaccine (Table 2, Fig. 1).

Similar results were obtained when including both definite and possible cases (adjusted OR = 0.56; 95% CI: 0.40–0.80) using the secondary time window (any HPV vaccine use prior to the index date; adjusted OR = 0.64; 95% CI: 0.49–0.83). There was no difference in the results between the type of vaccine used (HPV-16/18 or HPV-6/11/16/18).

## 4. Discussion

This follow-up study assessed the association between HPV vaccines exposure and ADs among French female adolescents and

young adults in the first 6.5 years of vaccination in France. Our results showed that, after adjusting for potential confounders, HPV vaccine exposure during predefine exposure time windows, did not increase the risk of CD/MS, CT, T1D, AT, or ITP all combined or taken separately. No conclusion could be drawn for GBS as no risk could be calculated. To our knowledge, this is the largest case-referent study assessing the risk of ADs associated with HPV vaccination available to date adding to the evidence that HPV vaccination does not increase the risk for ADs among young females, as reported in the cohort study conducted by the French drug safety agency (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*, ANSM) using data from the National Health Insurance database (*Système national d'information inter-régimes de l'Assurance maladie*, SNIIR-AM) [4].

Adverse reactions, such as ADs, have been reported following exposure to HPV vaccination [22]. Nonetheless, reports consisted mainly of case reports or case series without referent groups [6]. A study using data from the PGRx-AD information collection system has previously shown no evidence of an increased risk of ADs after exposure to the HPV-6/11/16/18 vaccine in females between the ages of 14–25 years [9]. Compared to this earlier publication, the present study followed more than double the number of participants, allowing increased statistical power, over a longer period of observation (6.5 years against 3.4 years in the first study); the included participants were also more diverse in terms of age and ethnicity.

Results of the present study are consistent with findings from



**Table 2**  
Association between HPV vaccines and definite cases of autoimmune diseases.

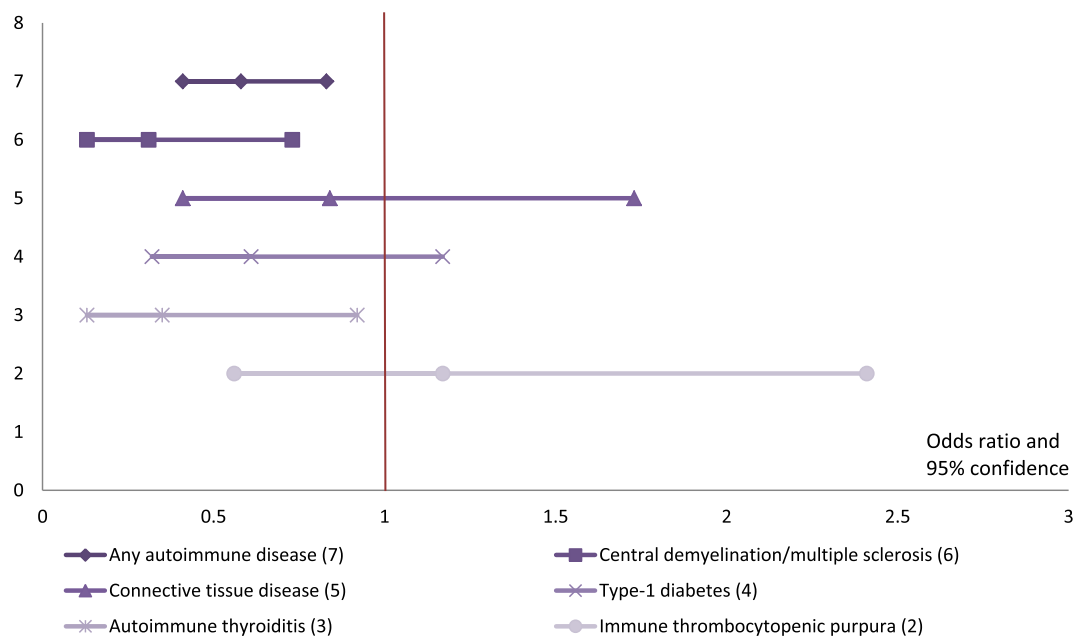
	Definite cases exposed <sup>a</sup> N (%)	Referents exposed N (%)	Crude OR (95% CI)	Adjusted OR <sup>b</sup> (95% CI)
<b>Autoimmune diseases (n cases/n controls)</b>				
<b>All combined (478/1869)</b>	52 (10.9)	421 <sup>c</sup> (22.5)	0.54 (0.38–0.75)	<b>0.58 (0.41–0.83)</b>
<b>Separately</b>				
Central demyelination/multiple sclerosis (113/863)	7 (6.2)	173 (20.0)	0.28 (0.12–0.64)	<b>0.31 (0.13–0.73)</b>
Connective tissue disease (92/769)	14 (15.2)	147 (19.1)	0.78 (0.40–1.52)	0.84 (0.41–1.73)
Guillain-Barré syndrome (13/130)	0 (0.0)	2 (1.5)	–	–
Type 1 diabetes (86/804)	14 (16.3)	189 (23.5)	0.56 (0.30–1.06)	0.61 (0.32–1.17)
Autoimmune thyroiditis (97/802)	6 (6.2)	126 (15.7)	0.28 (0.11–0.74)	<b>0.35 (0.13–0.92)</b>
Immune thrombocytopenic purpura (77/698)	11 (14.3)	87 (12.5)	1.18 (0.58–2.42)	1.17 (0.56–2.41)

Abbreviations: OR, odds ratio; CI, confidence interval.

<sup>a</sup> The number of cases and referents differ from the previous table as they are restricted to definite cases and their matched referents. Primary time window was  $\leq 6$  months before the index date for idiopathic thrombocytopenic purpura,  $\leq 42$  days for Guillain-Barré syndrome and  $\leq 24$  months for the other autoimmune diseases.

<sup>b</sup> OR obtained from conditional logistic regression adjusted for age, familial/personal history of autoimmune disease, parent's place of birth, and use of any oral contraceptives or vaccines (other than human papillomavirus vaccine) within 2 years before the index date.

<sup>c</sup> The total is inferior to the sum in the table as a referent could be matched to more than one case.



**Fig. 1.** Forest Plot displaying the odds (represented by the point effect estimate, OR, and 95% Confidence Intervals) of AD in association with exposure to HPV vaccines, across various autoimmune diseases.

large and well-controlled studies conducted by other groups [4,7]. The apparent protective effect observed from HPV vaccination has been previously reported [7,23] and may be explained in part by available information about a theoretical risk of AD that may have discouraged individuals with family history of AD to be vaccinated. Although not supported by any pertinent data at this time, a true protective effect cannot be ruled out either.

Precision of AD diagnoses was the main strength of the present study using the PGRx information system. The definition of each AD was based on international conventions and clinical data of cases were collected by board-certified specialists. Only 0.9% of initially recruited participants were rejected due to an unconfirmed diagnosis in the year following their recruitment. In addition, information regarding main exposure and potential risk factors was obtained through a validated and structured standardized telephone interview, administered by trained and qualified staff, blinded to the case/referent status. HPV vaccination status was obtained from patient reports and medical records with high level of agreement between both sources of information in cases and referents.

Another strength of the PGRx information system included minimization of a potential selection bias. All participants were first recruited in prospective ADs registries and later included in this analysis. Participating physicians and patients were blinded as to specific hypotheses regarding HPV vaccination. Furthermore, referent pools have been shown to be representative of the general population [24]. Cases and referents were similar for most socio-demographic and lifestyle characteristics, and multivariate analyses were adjusted for main potential confounders such as personal or family history of AD.

The use of PGRx allowed us to overcome important limitations that can be found in others databases. For example, in the UK *Clinical Practice Research Datalink* (CPRD), HPV vaccination recording is low, there is no standardized definition for diagnoses which are not systematically verified (possible misclassification of the disease), and risk factors such as family medical history, parental origin, smoking status or sociodemographic variables are not recorded [25]. Likewise, data elicited from the ASN study failed to capture any of the confounders ruled out in the present work due to lack of relevant clinical information. This shows that

the statistical power arising from the inclusion of a large number of subjects cannot always be translated into robust results that impact decision making.

Our results should be interpreted in the light of some limitations. First, despite the statistical power to detect a statistically significant association between HPV exposure and ADs overall, the very low prevalence of GBS in this population did not allow for risk evaluation. Second, a potential recall bias cannot be ruled out as information on co-medication, co-vaccination and other potential risk factors was collected through telephone interviewing of participants, going back 24 months earlier. Third, unmeasured and residual confounding may also introduce a distortion in results. For instance, information on the socioeconomic status of patients was partially lacking. Now, while lower rates of HPV vaccination were found in patients of low socioeconomic status [19], it is also possible for socioeconomic status to be associated with the development of AD [21]. Ethnicity was used here as a covariate as this has proven, at least partially, to be related to the socioeconomic status. Finally, our results must be interpreted with caution for comparable female populations of similar age, to the extent to which the French population can be considered comparable to other populations.

In conclusion, the ongoing surveillance of HPV vaccination using the PGRx information system showed no increased risk of ADs among young females. Continued vigilance and active surveillance are needed to confirm these findings for individual ADs.

#### Declaration of interest

LG-B reports grants received from the GSK group of companies and Sanofi Pasteur MSD during the conduct of the study and grants received from Hisamitsu, Johnson&Johnson Santé Beauté France SAS, Pfizer Santé Familiale, Laboratoires Urgo, Therabel Lucien Pharma, Zambon France, Sanofi-Aventis France, Laboratoires Bouchara-Recordati, Laboratoires Jolly-Jatel, Reckitt Benckiser Healthcare France, Novartis Pharma SAS, Coopération Pharmaceutique Française, Astra-Zeneca and Boehringer Ingelheim outside of the submitted work. IK-P reports personal fees received from AbbVie, Novartis and Sobi for consultancy and meetings outside of the submitted work. BG reports personal fees received from Sanofi during the conduct of the study. TP reports personal fees received from the GSK group of companies during the conduct of the study. PV reports personal fees and other fees for meeting registration, travel and accommodation from Biogen, Genzyme-Sanofi, Teva and Almirall and grants, personal fees and other fees for meeting registration, travel and accommodation from Merck, Novartis and Bayer outside of the submitted work. LA reports grants received from the GSK group of companies and Sanofi Pasteur MSD during the conduct of the study and grants received from Hisamitsu, Johnson&Johnson Santé Beauté France SAS, Pfizer Santé Familiale, Laboratoires Urgo, Zambon France, Sanofi-Aventis France, Laboratoires Bouchara-Recordati, Laboratoires Jolly-Jatel, Reckitt Benckiser Healthcare France, Novartis Pharma SAS, Coopération Pharmaceutique Française, Astra-Zeneca and Boehringer Ingelheim outside of the submitted work. MRo, AK, CL-F, JC, DB, CP, MN, P-YB, OF, NC-C, M-FC, J-FV, IB-V and GB report no conflicts of interest.

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the patient interviews, the statistical analyses and reporting of findings were all conducted independently of GlaxoSmithKline Biologicals SA, under the review of the Scientific Committee for this study.

#### Role of the funding source

GlaxoSmithKline Biologicals SA had no input into the design and conduct of the study or the reporting of results.

#### Trademarks

Cervarix is a trademark of the GSK group of companies. Gardasil is a trademark of Merck & Co., Inc.

#### Authorship statement

Authors L. Grimaldi-Bensouda, M. Rossignol, I. Koné-Paut, C. Lebrun-Frenay, C. Papeix, M. Nicolino, N. Costedoat-Chalumeau, B. Godeau, T. Papo, I. Bourgault-Villada, G. Breart, and L. Abenheim have made substantial contributions to the conception or design of the work, while contributing also, along with remaining authors A. Krivitzky, J. Clet, D. Brassat, P-Y. Benhamou, O. Fain, P. Vermersch M-F. Courcoux, and J-F. Viillard, to the acquisition, analysis, or interpretation of data for the work being submitted. All authors participated in the development and critical review, with important intellectual contributions, of the present manuscript. All authors had full access to the data and have approved the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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